American Journal of Hematology 55:199–204 (1997)

Feasibility, Toxicity, and Activity of LNH84-Derived Chemotherapy in the Management of Aggressive Lymphomas

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The results of chemotherapy remain unsatisfactory for many patients with advanced lymphomas. Both standard and more aggressive chemotherapy regimens might have their respective role in the management of theses diseases. We have tested the feasibility and assessed the toxicity and activity of a LNH84-derived chemotherapy for aggressive non-Hodgkin's lymphoma in two general hospitals. Thirty-three untreated patients were included over a period of 4 years. Median age was 39 years, 21 were male. International Working Formulation was F for 2 patients, G for 17, H for 8, I for 1, J for 4, one unclassified. Seventeen patients had B symptoms, 15 stage IV, 8 bulky disease, 21 abnormal LDH, 5 performance status ⩾2. The overall response rate was 93%. The single treatment related death resulted from bleomycin acute pneumonitis. Neutropenia WHO grade 4 occurred in all patients, resulting in infections grade 3 in 12 and thrombocytopenia grade 4 in 3. In the induction phase, courses could never be repeated day 14. The dose intensity of the four drugs contained in this phase is thus calculated between 64.5 and 81.5%. At 3 years, overall survival is 80% and event-free survival is 62%. This LNH84-derived regimen is effective. However, the induction phase is toxic and a 3-weekly interval appears more appropriate. Such intensive treatment might benefit patients with very aggressive lymphomas and this should be studied in randomized comparison against standard CHOP. Am. J. Hematol. 55:199–204, 1997. © 1997 Wiley-Liss, Inc.

Key words: non-Hodgkin's lymphoma; chemotherapy; treatment

INTRODUCTION

The significant advance observed in the management of aggressive non-Hodgkin's lymphomas (NHL) is the result of the development of effective combination chemotherapy [1]. A complete remission rate of 45 to 55% is obtained using first-generation chemotherapy and this will eventually translate into cure for one-third of the patients [2]. Over the past 20 years, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone, best known as CHOP, has become the standard treatment. However, despite its activity, most patients will eventually relapse and die of the NHL as a result of acquired or inherent resistance of lymphomatous cells or inability to deliver the planned cytotoxic dosage. In order to circumvent these limitations, alternating non-cross-resistant chemotherapy combinations following dose-intensity concepts have been developed [3,4].

Second- and third-generation chemotherapy combinations provided a better remission rate and pretended to better cure rate. Both LNH80 and LNH84 belong to this category and were based on a rapid succession of 3 courses of intensive chemotherapy followed by a consolidation phase with non-cross-resistant agents [5,6].

Only recently has the standard first-generation CHOP combination been randomly compared against second- and third-generation chemotherapy. Somehow disappointingly, the first analysis of this SWOG trial failed to show any statistically significant difference in response rate or survival [7].

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Received for publication 19 August 1996; Accepted 28 March 1997.

TABLE I. LNH-84 Derived Induction Phase Chemotherapy (ACVBP)*

			Day				
			1	2	3	4	5
Bleomycin	10 mg TD	iv	■				■
Cyclophosphamide	1,250 mg/m^2	iv	■				
Doxorubicin	75 mg/m^2	iv	■				
Vincristine	1.4 mg/m^2	iv	■				■
Prednisone	60 mg/m^2	po	■	■	■	■	■
Methotrexate	15 mg TD	it			■		

*q 14 days × 3.

TABLE II. Consolidation Phase of the LNH-84

		Week							
		9	10	12	14	16	17	19	21
Methotrexate	3 g/m^2 iv D1	■	■						
Ifosfamide	1.5 g/m^2 iv D1			■	■				
Etoposide	300 mg/m^2 iv D1			■	■				
Asparaginase	50,000 Ul/m^2 iv D1					■	■		
Cytarabine	100 mg/m^2 s/cut D1 to 4							■	■

We have routinely used a LNH84-derived combination over the past years in the setting of two general hospitals and our experience is reported here with emphasis on feasibility and toxicity.

MATERIALS AND METHODS

Patients

Between July 1990 and September 1994, 33 consecutive and previously untreated patients with aggressive lymphomas entered this study. Eligibility criteria were age below 65 years and histology F to J according to the International Working Formulation [8]. Staging at entry included medical history, physical examination, chest X-ray, abdominal ultrasound, and/or thoracic-abdominal CTscan. Bone marrow aspirate with biopsy and lumbar puncture with cerebrospinal fluid examination were also obtained. Laboratory studies included full blood count, electrolytes, proteins, creatinine, and lacticodehydrogenase. Patients were seen at least once weekly during treatment or hospitalized during courses of treatment. After the treatment had been completed, patients were seen on a monthly basis for 3 months, then every 3 months for 1 year, and finally every 6 months.

Chemotherapy

The LNH84-derived combination initially differed from the original LNH84 by the substitution of vindesine in the induction phase with the less myelotoxic vincristine at a dose of 1.4 mg/m^2 (maximum 2 mg) (Table I). Another reason for such substitution is that vindesine was not reimbursed by our social insurance system. Eight patients thus received vindesine whereas the 25 others received vincristine.

In the consolidation phase, unfortunately only 6 patients were fully treated according to the original LNH84 protocol (Table II). The other 27 patients received various consolidations out of the original protocol but with roughly similar total doses and timing. Actually, etoposide was given to 18 of these patients at a total dose of 800 mg/m^2, methotrexate to 17 at 6 g/m^2, cytarabine to 16 at 800 mg/m^2, ifosfamide to 8 at 3 g/m^2, and asparaginase to 1 at 100,000 Ul/m^2. Furthermore, one patient received one additional course of a combination of etoposide, cytarabine, BCNU, and bleomycine and 1 patient received one course of DHAP. Four patients received 3 additional courses of ACVBP as consolidation and 1 patient received 3 courses of standard CHOP-bleomycine.

Response

After 3 courses of ACVBP, response was assessed for the first time. A fourth course of ACVBP was administrated to patients not achieving a complete remission. Patients not responding or progressing during ACVBP were switched to a salvage second-line treatment. Overall response was finally assessed at the end of chemotherapy. Complete remission (CR) was defined as the disappearance of all abnormalities, partial remission (PR) as a reduction of more than 50% of each site of measurable disease, and no response (NR) or progressive disease (PD) as anything else. NR and PD were, therefore, defined as primary resistant disease. Patients with no measurable disease or in CR after initial surgery were not considered evaluable for response.

Statistics

Survival was calculated from day 1 of the treatment with the method of Kaplan-Meier [9]. Small numbers did not allow for other pertinent statistical analysis.

Supportive Care

Prophylactic antibodies and hemopoietic growth factors were not routinely used. Packed red cell transfusions were given as clinically indicated and platelets were given in case of a thrombocytopenia below 20×10^9/L. Blood products were irradiated in all cases.

RESULTS

Patients

Thirty-three patients were treated. 21 were males. Median age was 39 years (range 15–61) and 28 had a WHO performance status of $\leqslant 1$. 17 patients had B symptoms. Twenty-nine were of B phenotype whereas 4 were T. Seventeen patients had diffuse large cell lymphoma (G),

TABLE IIIa. Toxicity of ACVBP Induction (Per Patient)

	WHO grade		
	2	3	4
Leucopenia	0	9	24
Neutropenia	0	0	33
Infections	4	12	0
Thrombocytopenia	5	1	3
Lung	0	1	0
Neuropathy	4	3	0
Vomiting	5	4	0
Mucositis	10	3	0

TABLE IIIb. Haematological Toxicity of the Various Consolidations (Per Patient)

	WHO grade			
	1	2	3	4
Leucopenia	1	7	9	6
Neutropenia	2	2	4	10
Anemia	8	9	3	0
Thrombocytopenia	4	4	1	5

2 diffuse mixed (F), 8 large cell immunoblastic (H), 1 lymphoblastic (I), 4 Burkitt or Burkitt-like (J), and 1 remained unclassified. Ann Arbor clinical stage was I in 7 cases, II in 6, III in 5, and IV in 15. Bulky tumor (>10 cm) was present in 8 patients, 21 patients had an abnormal LDH, and 23 patients had extranodal involvement. According to the International Prognostic Index, 16 patients were in the low-risk group, 9 in the low-intermediate, 7 in the high-intermediate, and one in the high-risk group [10].

Toxicity

One hundred eight of the ACVBP induction were administered. One patient received only 1 course, 2 patients 2 courses, 17 patients 3 courses, and 13 patients 4 courses. One treatment-related sudden death occurred in a patient with a biopsy-proven bleomycin-induced pneumonitis. Myelosuppression was severe with neutropenia WHO grade 4 occurring in all patients. Twelve patients received packed red cells and 2 of them also platelets. Alopecia was universal. Infection WHO grade 3 occurred in 12 patients requiring hospitalization and iv antibiotics. Peripheral neuropathy grade 2 occurred in 4 patients and grade 3 in 3 (Table III). Planned interval between courses of ACVBP was 14 days. However, 17 days were necessary between courses 1 and 2, 18 days between courses 2 and 3, and 21 days between courses 3 and 4. Dose intensity of ACVBP varied between courses from 64.5 to 80.5% for vinca alcaloids, 65.7 to 81.5% for doxorubicin, 66.0 to 79.6% for cyclophosphamide, and 66.7 to 81.5% for bleomycin (Table IV). Median length of hospital stay during the induction phase was 18 days (range 2–42). No serious toxicities occurred during the consolidation phase (Table III) but 4 patients received packed red cells and 1 of them also platelets.

Response

Thirty patients were evaluable for response. After 3 to 4 courses of ACVBP, 12 patients achieved a CR and 16 a PR for an overall response rate of 93%. Seven patients in PR further responded to achieve CR after the consolidation phase (Table V). However, one patient in CR and 1 patient with no measurable disease progressed during this phase. At the end of chemotherapy, 6 patients received adjuvant involved field radiation therapy in CR or in PR. Five patients received additional high-dose consolidation chemotherapy with hemopoietic stem cell rescue in first CR. Two patients with residual masses on CT scan underwent a negative exploratory laparotomy.

Relapse/Progression

Nine patients have relapsed. Five patients relapsed from CR, 3 progressed from PR, and 1 from no measurable disease. Seven relapses occurred in initially involved sites and 2 in other sites. Five patients relapsed in both involved and uninvolved sites. One patient suffered CNS progression despite high dose iv and prophylactic i.t. methotrexate. Relapsing patients received second-line chemotherapy. Four patients obtained a second CR, and 3 of them were further consolidated with high-dose chemotherapy and bone marrow rescue. Five patients did not respond to salvage therapy and died with PD.

Survival

Overall survival is 79% (95% CI = 59–91) and event-free survival is 62% (95% CI = 39–77) at 3 years (Fig. 1). Two patients died in the low-risk category group, 2 in the low-intermediate, and 3 in the high-intermediate (Table VI).

DISCUSSION

We have evaluated the feasibility and efficacy of treating malignant lymphomas with a LNH84-derived combination chemotherapy. Although the complete remission rate of the induction phase of our combination (40%) is lower than reported with the original LNH84 (75%), or with M(or m)-BACOD (65%), MACOP-B (84%), ProMACE-CYTABOM (79%), COP-BLAM III (84%), and ProMACE MOPP (76%), both the overall response rate (93%) and the survival rate (65%) at 3 years are comparable [6,11–15]. At a median follow-up of 36 months, 26 patients are alive with 21 free from lymphoma progression. The median age of our population is only 39 years and this might be taken as a favourable selection bias. This can also be considered as an incidental trend in the

TABLE IV. Dose Intensity of ACVBP Induction (Percentage of Drug Given Per Week)

	Course 1		Course 2		Course 3	
Bleomycin	78.4%	7.84 mg/w	81.5%	8.15 mg/w	66.7%	6.67 mg/w
Cyclophosphamide	77.6%	465.6 mg/m^2/w	79.6%	477.6 mg/m^2/w	66.0%	395.9 mg/m^2/w
Doxorubicin	77.6%	29.1 mg/m^2/w	80.3%	30.1 mg/m^2/w	65.7%	24.7 mg/m^2/w
Vincristine (vindesine)	80.6%	1.13 mg/m^2/w	80.2%	1.12 mg/m^2/w	64.5%	0.92 mg/m^2/w

TABLE V. Response to Treatment

	ACVBP induction		Various consolidations
Complete response	12	→	18
Partial response	16	→	8
Not evaluable	3	→	2
Progressive disease	2	→	2
Total (patients)	33		30

referring process during the period in which the study was conducted.

The discrepancy between CRs and survival in our study is due to the persistent radiological abnormalities on CTscan. These are likely to be seen in cases of high initial tumour burden. Indeed, half of the patients were stage IV and 8 had bulky disease. In two cases a radical surgery was done after treatment for diagnostic purposes and this showed fibro-necrotic tissue with no malignant cells. In addition, most of the radiological PR patients are alive and free from progression and this is taken as another indication of the absence of active tumour after treatment despite residual abnormalities. A longer follow-up is, however, necessary to confirm this hypothesis and assess the program's impact.

One of the characteristics of the LNH84 regimen is the separation into an intensive induction followed by a consolidation phase with non-cross-resistant agents. However, the evidence is still lacking for the absence of cross-resistance between cyclophosphamide (induction) and ifosfamide (consolidation). Moreover, the dose of ifosfamide is kept rather low in the original LNH84 protocol and the drug is administered only once. This is not in accordance with the way such a drug should be optimally given [16]. Similarly, etoposide is more active when administered on repeated days [17] whereas this is not the case in the consolidation phase of LNH84. We, therefore, altered most of the consolidation phase but this major deviation doesn't appear to have either negatively or positively influenced the results. Such a consolidation regimen would be very difficult to reproduce from one patient to another.

Eleven patients have relapsed or progressed, all but 2 during the first year of treatment, thus suggesting initial chemoresistance. Four of these patients achieved a second CR and 3 of them were further consolidated with high-dose chemotherapy and stem cell rescue and are free from progression. Results from the PARMA study have confirmed a better outcome for patients receiving high-dose chemotherapy in first relapse [18] but an earlier application of this approach to patients at high risk of treatment failure remains an open question. In our study, however, 5 patients with poor prognostic features at presentation successfully underwent such a procedure.

Seven patients relapsed in initially involved sites and only one of them had received adjuvant radiation therapy at the site of relapse. This further supports recent studies of additional radiation therapy since the 5 other patients who were actually irradiated have not relapsed [19]. Six patients died of progressive disease but only 1 had true resistant disease ab initio. Age and LDH appeared the only predictors of failure in our small group of patients but this was not tested statistically because of small numbers. A seventh patient died as a result of a respiratory arrest shortly after the diagnosis of a bleomycin-induced lung toxicity.

Myelosuppression of ACVBP was severe with agranulocytosis in all patients, requiring intravenous antibodies in one-third of them. Despite the lack of evidence of increased treatment efficacy [20], an appropriate use of hemopoietic colony stimulating factors could have shortened the total hospital stay of 18 days per patient we actually observed [21]. In our hands, ACVBP could not be recycled as planned on day 14 not only because of myelotoxicity but also because of fatigue. Dose intensity was thus lower than planned in the original protocol. However, drug dosage was not reduced and patients tolerated almost 100% of the prescribed drugs. Only vincristine had to be significantly lowered because of dose-limiting neurotoxicity. We were, therefore, not capable of decreasing the myelotoxicity of ACVBP and, on the contrary, we added an additional toxicity by substituting vindesine with vincristine. This limiting neurotoxicity did not occur in patients treated with vindesine. However, numbers are too small to allow a pertinent comparison between these patients and to discuss differences in overall outcomes.

Until undisputable evidence of better cure rate, an intensive combination like the one presented here should be administered to a limited number of patients given its high toxicity. A randomized study could perhaps be done in those patients at high risk of treatment failure in the high-intermediate and high-risk groups. These patients might even benefit from high-dose chemotherapy with stem cell rescue in first complete or partial remission and

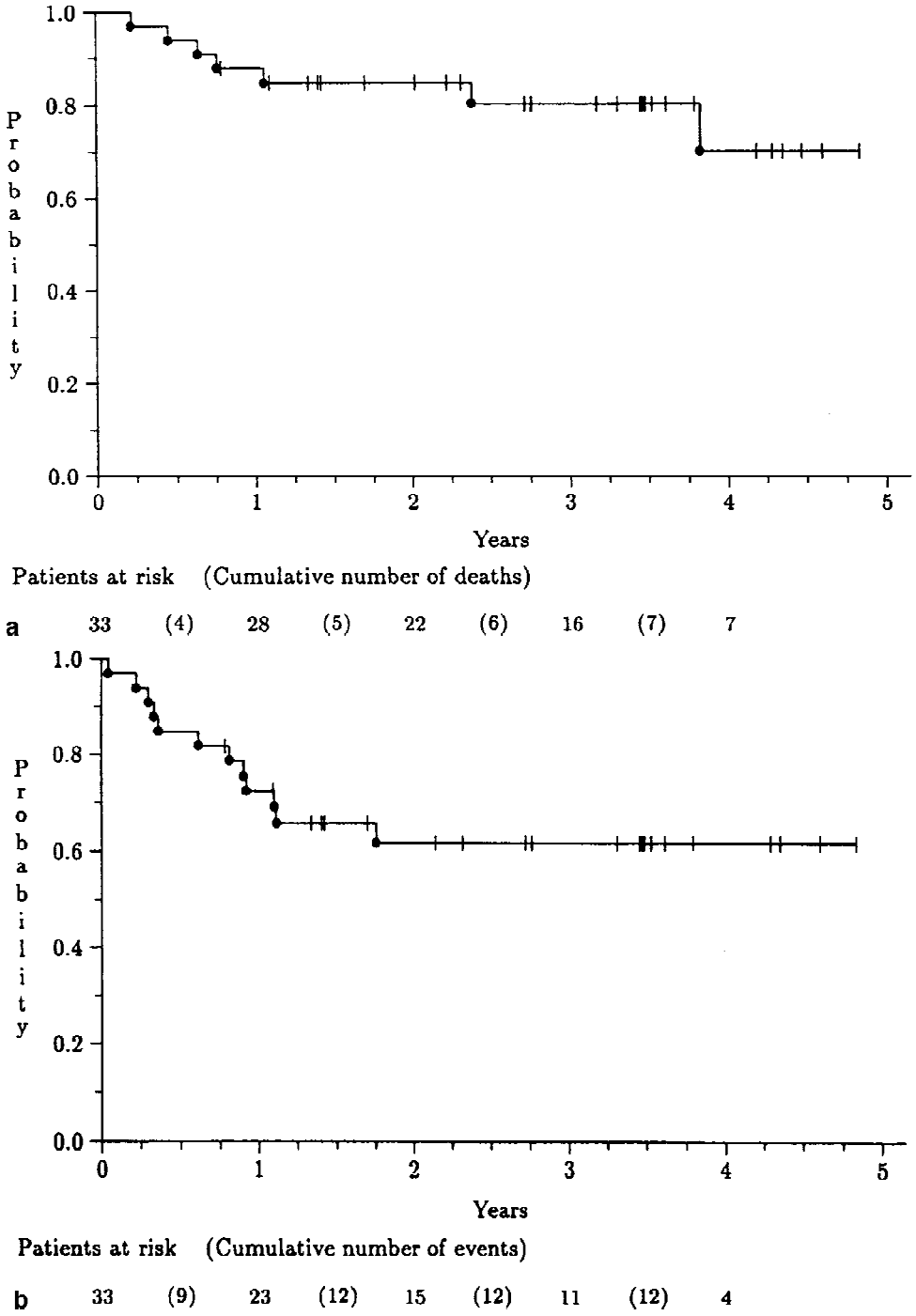

Fig. 1. a. Overall survival. b. Event-free survival.

TABLE VI. Survival According to the International Prognostic Index

	No. of patients	Relapse-free survival	Overall survival
Low	16	12	14
Low intermediate	9	5	7
High intermediate	7	3	4
High	1	1	1
Total	33	21 (64%)	26 (79%)

such studies are in progress. Other patients will still be treated optimally with standard CHOP.

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